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Clinical and biochemical indicators of disease severity and neurological findings in COVID-19: A study of King Edward Medical University (KEMU), Pakistan

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Abstract: This study investigated the significance of difference between presence and absence of different neurological findings in COVID-19, in relation with the biochemistry. Various significant correlations in connection with the disease severity and clinical factors were also identified. 351 COVID-19 patients were included. Different laboratory/ clinical findings were investigated. Correlations Kendall's tau and Pearson Chi-Square were applied to find the correlations between severity and clinical findings. The Mann-Whitney Test was applied for a comparison between two types of neurological groups for each biochemistry parameter. Headache was reported in 28% and dizziness in 13% patients. The impaired smell and impaired taste were reported in 28.5% and 36.2% patients, respectively. The muscle pain was present in 39% patients. 80% patients had low lymphocytes & 70% had high neutrophils. 54.5% were found with high ALP. LDH was elevated in 73%. Severity was found significantly correlated with decreased oxygen saturation, age and raised levels of urea, creatinine and LDH. The groups (with/without CNS involvement) were statistically different in ALP, groups (with/without PNS involvement) in WBC, lymphocytes, neutrophils, ALP, urea, creatinine, CK, CKMB and LDH and groups (with/without MSK involvement) in WBC. Oxygen saturation, age, urea, creatinine and LDH are significant indicators of disease severity in COVID-19. The altered levels of different biochemistry can impact the neurological states of COVID-19 patients.

Keywords: COVID-19, central nervous system, disease severity, LDH, ALP, lymphocytes, oxygen saturation.

INTRODUCTION

A comprehensive evaluation for the clinical features and neurological manifestations along with the association of the laboratory findings in 351 symptomatic COVID-19 patients was performed. This study identified various significant correlations in connection with the disease severity levels (mild, moderate, severe and critical) and the clinical factors as well as the altered biochemistry levels. The world is facing challenging times due to the recent pandemic coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) preceded by the severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS) in 2012 (Silva *et al.,* 2020). Like SARS and MERS, COVID-19 frequently presents similar symptoms of as a pneumonia such as fever, fatigue, dry cough and dyspnea, occasionally accompanied by diarrhea, coupled with recent exposure and having new pulmonary infiltrates on chest radiography (Guan *et al.,* 2020). Coronavirus infections have been associated with numerous neurological manifestations such as: stroke, seizures, encephalopathy, encephalitis, acute myelitis and neuropathy (Desforges *et al.,* 2020). It is known that angiotensin-converting enzyme 2 (ACE2) is the main host cell receptor of SARS-CoV-2 concentrated in the alveolar epithelial cells; it also exhibited in other tissues, such as kidney, intestine, blood vessels, and heart (Zhao *et al.,* 2020a). Since ACE2 is expressed in motor cortex, cytoplasm of neurons, glial cells, and sympathetic pathways in the brainstem (Xia and Lazartigues, 2008), COVID-19 may also present with neurological manifestations via two pathways (Li *et al.,* 2020), i.e., direct infiltration of the brain through the nasal epithelium and entrance into the olfactory pathway via. retrograde trans-synaptic spread, which explains the loss of smell and taste in the early-phase, while hematogenous spread following pulmonary infection is thought to result from the widespread homeostatic dysregulation and cytokine storm causing pulmonary, renal, hepatic and cardiovascular injury and secondary neurological manifestations of COVID-19 (Baig *et al.,* 2020). Severe levels of COVID-19 infection are associated with raised D-dimers, increased lactate dehydrogenase (LDH), alanine aminotransferase (ALT) & aspartate aminotransferase (AST) levels, as well as the elevated values of urea, creatinine, creatine kinase (CPK) and creatine kinase-MB (CK-MB) (Zhang *et al.,* 2020a; Chen

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et al., 2020a). Mao *et al.,* (2020) reported lower levels lymphocyte and platelets in COVID-19 patients reported with CNS manifestations compared to those without CNS involvement; similarly, significantly higher levels of CPK were present in patients with MSK involvement. Systemic inflammation due to COVID-19 infection causes the migration of activated macrophages into the brain via the blood brain barrier (BBB), which causes a cytokine storm (Yachou *et al.,* 2020) resulting in meningitis, encephalitis, myelitis and promoting atherosclerosis and thrombosis, which significantly increase the risk of acute cerebrovascular disease. In addition, a molecular imitation between the specific viral proteins and gangliosides causing a bystander attack against the axon, is the likely mechanism behind the peripheral nervous system manifestations like in the Guillain–Barré syndrome. Following neurological features encephalopathy, corticospinal tract dysfunction, agitation and delirium, were reported from a study conducted in France: (Helms *et al.,* 2020).

MATERIALS AND METHODS

Study design and setting

A prospective, cross-sectional study was designed to investigate the clinical and neurological manifestations of the symptomatic COVID-19 patients (n=351) from four medical wards, including intensive care units (ICU) of King Edward Medical University (KEMU), Mayo hospital, Lahore Pakistan from 15th May - 15th July, 2020. In all patients, real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assays of nasopharyngeal samples were positive for SARS-CoV-2. All symptomatic COVID-19 patients of both genders between 18-80 years were included with written and informed consents. The study was conducted after the ethical approval (356/RC/KEMU) from the IRB (Institutional Review Board)/ASRB (Advanced Studies and Research Board).

Background, clinical and neurological records

The segregation of the severe and critical cases was done as per guidelines of the World Health Organization (WHO). Information collected for demographic and clinical data through a proforma. Neurological manifestations were categorized into three main domains: central nervous system (CNS), peripheral nervous system (PNS) and musculoskeletal (MSK). Impaired consciousness included the change of consciousness level (somnolence, stupor, and coma) and consciousness content (confusion and delirium). Acute cerebrovascular disease including both ischemic and hemorrhagic was diagnosed by clinical history and brain computed tomography (CT). Skeletal muscle injury was considered as when a patient has a muscle pain with a serum creatine kinase level (greater than 200 U/L). All neurological symptoms were reviewed expert neurologists.

STATISTICAL ANALYSES

Kendall's tau and Pearson chi-square tests

IBM SPSS (2020) was used to determine the correlations through The Kendall's tau (τ) and Pearson Chi-Square tests were evaluated between 'the severity levels with the following the cofactors: Age, gender, source of infection, SpO_2, outcome, D-dimers, CBC/LFT/RFT and tissue markers. Correlation coefficients Phi (Φ) and Cramer's V values were calculated.

Neurological comparisons with respect to biochemistry

Two groups of patients were created in each neurological involvement (CNS/PNS/MSK). One group was with the indication of CNS/PNS/MSK, while the other group was without the indication of them. The Mann-Whitney U test was applied to develop a comparison between these groups for each type of biochemistry parameter.

RESULTS

Background & clinical information

More male patients (59%) acquired COVID-19 infection than the female patients (41%). Mean age of the patients was 47.94±15.84 years. Maximum (140; 40%) patients were found in the age range 36-55 years. More patients (247; 70.4%) were belonged to urban areas. There was more incidence of mild cases (133; 38%) than the moderate to critical cases. 59(16.8%) patients were reported in critical condition. The mean onset of the infection was 4.39 days. The majority (215; 61.3%) of the patients were reported 1-4 days of the infection onset. More patients (147; 42%) patients were having oxygen saturation (SpO_2) less than 90%, falling into severe infection cases. The majority (222; 63.2%) of the patients were with the call score <6. The majority (140; 40%) of the patients was having normal chest X-ray, whereas 33.6% were having more than 50% of lung parenchymal involvement. Majority (267; 76%) of the patients had normal ECG, however, 10% were found with ischemic changes. The major (167; 47.6%) source of infection was the family. Infection from the social gathering was 25.6%, and from the international travel was 10.5%. 16.2% infection was found in healthcare workers. The survival rate was 81.2% and the death was reported in 18.8% patients.

Typical symptoms, comorbidities and post-infections

Following were the common typical symptoms reported: fever: 88%; shortness of breath (SOB): 53% and cough: 43.6%. Most of the infected patients (177; 50.4%) did not present any comorbidity. However, 117(33.3%) patients were diabetic and hypertension was reported in 120(34.2%) patients. Only 11% patients were found with cardiovascular disease (CVD). Moreover, only about 2% patients had pulmonary disease or liver disease. Majority patients (200; 57%) did not report any complication due

Table 1 (a): Kendall's Tau (b) (τ) Correlation (Dependent variable= Severity Level; Independent variables: Age, SpO_2, CBC/LFT/RFT parameters, Tissue Markers)

Correlation	Correlation Coefficient	p value	Correlation Coefficient Level
Severity & Age	0.335	0.000*	Moderate, positive
Severity & SpO_2	-0.806	0.000*	Strong, negative
Severity & WBC	0.266	0.000*	Weak, positive
Severity & Lymphocytes	-0.174	0.000*	Weak, negative
Severity & Neutrophils	0.193	0.000*	Weak, positive
Severity & Hemoglobin	0.101	0.013*	Weak, positive
Severity & ALT	0.236	0.000*	Weak, positive
Severity & AST	0.231	0.000*	Weak, positive
Severity & Urea	0.338	0.000*	Moderate, positive
Severity & Creatinine	0.405	0.000*	Moderate, positive
Severity & ALP	0.164	0.000*	Weak, positive
Severity & LDH	0.411	0.000*	Moderate, positive
Severity & CK	0.255	0.000*	Weak, positive
Severity & CKMB	0.290	0.000*	Weak, positive

*Highly significant (p value<0.050)

Table 1(b): Pearson Chi-Square Test χ^2 (severity levels & gender, outcome, source of infection & D dimers)

Correlation	Pearson Chi-Square	df	*p* value	Phi	Cramer's V
Severity & Gender	44.498	3	0.000*	0.356	0.356
Severity & Outcome	146.713	3	0.000*	0.647	0.647
Severity & Infection Souce	50.739	9	0.000*	0.380	0.220
Severity & D Dimers	109.582	3	0.000*	0.559	0.559

*Highly significant (p value<0.050)

to COVID-19 infection. However, 63(18%) patients were found with ALI (acute liver injury), 52(14.8%) were with ARI (acute renal injury) and myocarditis was present in 42(12%) patients.

Neurological manifestations-
CNS, PNS and MSK involvements

The majority of the patients (206; 58.7%) did not report any CNS involvement. However, 99(28.2%) patients reported headaches, 46(13.1%) reported dizziness and 15(4.3%) reported impaired consciousness. Similarly, the majority of the patients (188; 53.5%) did not report PNS involvement. However, impaired taste was reported in 127(36.2%) and impaired smell was reported in 100(28.5%) patients. Likewise, the majority of the patients (211; 60%) did not report any MSK involvement. However, the muscle pain was reported in 136(38.7%) patients.

Biochemistry laboratory investigations

Mean value of neutrophils (80.20±39.41%) of all patients was found higher than the normal. White blood cells (WBC) were not found disturbed in most of the patients (206; 58.7%), however, 25% showed high WBCs. Most of the patients (281; 80.1%) were found with low lymphocytes. More patients (244; 69.5%) were found with high neutrophil values. Hemoglobin was found low in 213(60.7%) patients. Around 80% of patients were having normal values of platelets. The mean values of AST, ALP and Urea were found higher than the normal range. The mean values were as follows: AST: 53.84±74.41U/L, ALP: 177.05±71.22U/L, urea: 51.50±56.36mg/dL and creatinine: 1.83±5.54mg/dL. Most of the patients (276; 78.6%) were found with normal ALT values, however, 75(21.4%) were having high ALT values. Most of the patients (229; 65.2%) were found with normal AST values, however, 122(34.8%) were having high AST values. More patients (191; 54.5%) were having high values of ALP as compared to the patients who had normal ALP values. Most of the patients (277; 78.9%) were found with normal urea values, however, 74(21.1%) were having high urea values. The majority of the patients (283; 80.6%) were found with normal creatinine values, however, 63(17.9%) were having high creatinine values. Almost all patients (98%) were having normal values of bilirubin. Mean values of CK -creatine kinase (198.23±226.09 U/L) and LDH (478.36±340.91 U/L) were found higher than the normal range. Most of the patients 220(62.7%) were found with normal CK values, however, 131(37.3%) were having high values of it. Similarly, most of the patients (264; 75.2%) were having normal values of CKMB (creatine kinase-MB), however, 87(24.8%) were having high values of it. The majority of the patients (255; 72.6%) were having high values of LDH (lactate dehydrogenase), only 27% patients had normal LDH. Most of the patients (264; 75.2%) were having normal D-dimers.

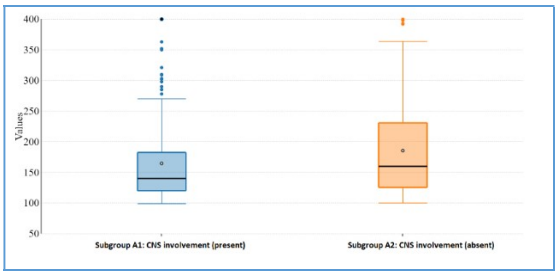

Fig. 1(a): Comparison of ALP between groups of CNS involvement

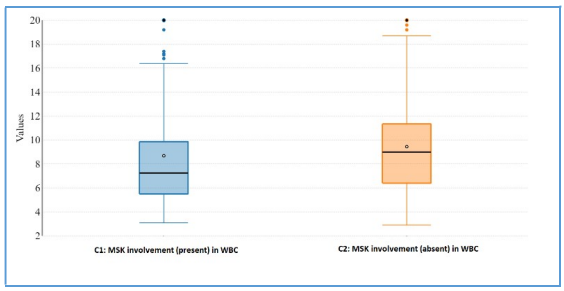

Fig. 1(b): Comparison of WBC between groups of MSK involvement

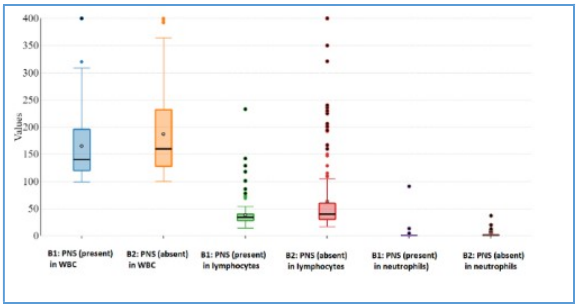

Fig. 1(c): Comparison for CBC Parameters between groups of PNS involvement

Kendall's tau (τ) correlations

All correlations with severity level were found statistically significant (table 1(a)). The severity level was found in significant correlation (p value< 0.050) with age, oxygen saturation, WBC, lymphocytes, neutrophils & hemoglobin, ALT, AST, ALP, urea, creatinine & bilirubin, CK, CKMB & LDH. The significant correlation was found strong, negative with the decreased oxygen saturation (SpO_2), whereas moderate, positive correlations were found with urea, creatinine and LDH (lactate dehydrogenase). Rest of all correlations were weak association.

Pearson chi-square correlations

All correlations with severity level were found statistically significant (table 1(b)). The severity levels were found in significant correlation with gender, outcome (survival/death), source of infection and D dimers (raised/normal).

Stratification of severity levels in different factors

More male patients (n=61) were in critical cases as compared to female patients. The majority of female patients (n=82) were reported mild cases. More mild cases (n=132) were survived, whereas more critical patients (n=41) were died. There were more (n=133) normal D dimers in the mild cases, whereas, more raised D dimers were reported in severe (n=39)-critical cases (n=36). More mild (n=51) and severe (n=52) cases were reported due to the contact with the family members as compared to other sources of infection. However, 42 mild cases were also reported in the health workers.

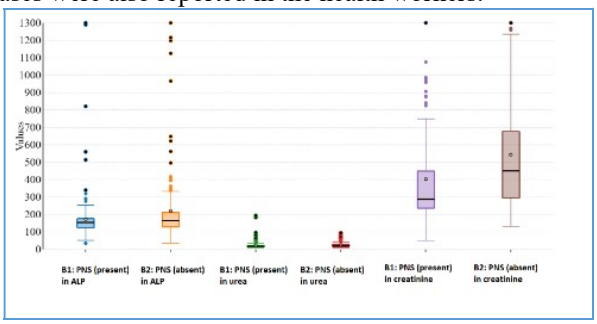

Fig. 1(d): Comparison for LFT/RFT Parameter (between groups of PNS involvement

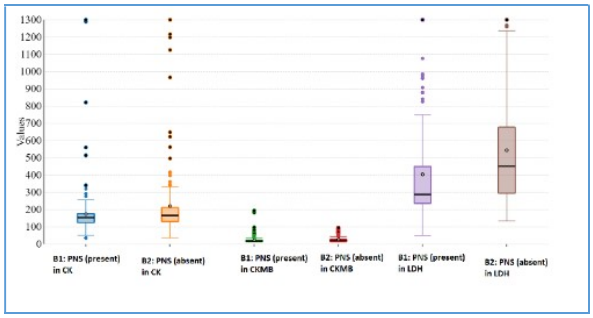

Fig. 1(e): Comparison for tissue marker parameter between groups of PNS involvement

Comparisons of neurology in biochemistry

The subgroups of CNS were only found statistically different in ALP (p-value: 0.00424). The subgroups of PNS were found statistically different in following biochemistry parameters: WBC, lymphocytes, neutrophils, ALP, urea, creatinine, CK, CKMB and LDH with p-values<0.050. The subgroups of MSK category were only found statistically different in WBC (p-value: 0.00652) (table 2). Graphical comparisons are shown in figs. 1(a-e).

DISCUSSION

The current research identified significant correlations in connection with the disease severity and clinical features as well as with the deranged biochemistry. In a study from China, 36% COVID-19 patients developed following neurological manifestations: CNS (24.8%), PNS (8.9%) and MSK (10.7%). These patients were inclined to severely affected, especially in old age, having comorbidities to have neurological complications from COVID-19. In patients with CNS involvement, the common symptoms were dizziness (16.8%) and headache

(13.1%) and with PNS involvement, the most common reported symptoms were impairment of taste (5.6%) and smell (5.1%) (Mao *et al.,* 2020). It has been postulated that excessively elevated lactate dehydrogenase (LDH) due to surplus cell damage in COVID-19 infection, results in a significant reduction of oxygen-carrying capacity of RBCs and transport of oxygen to the tissues causing an ischemic hypoxic state leading to musculoskeletal pain. In addition, the increase in growth factors, cytokine levels, and micro-vascular changes can also trigger pain by over-expression of the dorsal root ganglion (Kucuk *et al.,* 2020). One laboratory sign of an early infection without fever and cough during the incubation phase is the development of lymphopenia. When the neurological symptoms occur, the lymphocyte count should be monitored routinely (Zhou *et al.,* 2020). Alkaline

Table 2: Mann-Whitney U Test. Comparison between Three Groups (A=CNS, B=PNS & C=MSK) for Biochemistry

Laboratory Findings	Group A- CNS Involvement Subgroup A1: CNS Present; Subgroup A2: CNS Absent			
	Parameters	U score	Z score	p value
CBC	WBC	13267.5	1.74959	0.08012
	Lymphocytes	14894.5	-0.00962	0.99202
	Neutrophils	14111	0.84752	0.39532
	Hemoglobin	13969.5	0.99885	0.31732
	Platelets	14042	0.92132	0.35758
LFT/RFT	ALT	14783.5	-0.12833	0.89656
	AST	14738	0.17699	0.85716
	ALP	12227	0.86233	0.0042*
	Urea	13805	1.17477	0.242
	Creatinine	14643	0.27859	0.77948
	Bilirubin	16238.5	1.540474	0.123445
Tissue Markers	CK	13814.5	1.16461	0.24604
	CKMB	13861	1.11488	0.267
	LDH	14212.5	0.73898	0.4593
Group B- PNS Involvement Subgroup B1: PNS Present; Subgroup B2: PNS Absent				
	Parameters	U score	Z score	p value
CBC	WBC	12803	2.65637	0.00782*
	Lymphocytes	12599	-2.8715	0.0041*
	Neutrophils	11848	3.66365	0.00026*
	Hemoglobin	13991.5	1.40281	0.16152
	Platelets	14568.5	0.79422	0.42952
LFT/RFT	ALT	13462	1.96129	0.05
	AST	14015.5	1.37749	0.16758
	ALP	12741	2.72176	0.00652*
	Urea	11121	4.43045	0.00001*
	Creatinine	10636.5	4.94147	0.00010*
	Bilirubin	15751	-0.551720	0.581140
Tissue Markers	CK	12844.5	2.6126	0.00906*
	CKMB	12295.5	3.19165	0.00142*
	LDH	10252	5.34702	0.00001*
Group C- MSK Manifestation Subgroup C1: MSK Present; Subgroup C2: MSK Absent				
	Parameters	U score	Z score	p value
CBC	WBC	12237.5	2.72006	0.00652*
	Lymphocytes	13539.5	-1.32135	0.18684
	Neutrophils	13973	0.85566	0.38978
	Hemoglobin	14402.5	0.39426	0.69654
	Platelets	13942	0.88896	0.37346
LFT/RFT	ALT	14182	0.63113	0.5287
	AST	14721	0.0521	0.96012
	ALP	13905.5	0.92817	0.35238
	Urea	13686.5	1.16344	0.24604
	Creatinine	14703	-0.07144	0.9442
	Bilirubin	14001.5	0.730471	0.465103
Tissue Markers	CK	13165.5	-1.72313	0.08544
	CKMB	13778	1.06514	0.28462
	LDH	13316.5	-1.56092	0.11876

*Highly significant (p value< 0.050)

phosphatase (ALP) used to present on the neuronal membranes and plasma ALP activity raises in brain insults. This suggests that plasma ALP can indicate the neuronal loss (Kellett *et al.,* 2011). The severe COVID-19 patients with CNS involvement present with reduced lymphocyte, reduced platelet counts and high urea levels as compared with those without CNS involvement. The patients can have higher neutrophil and lower lymphocyte counts, and higher D-dimer levels (Mao *et al.,* 2020). The raised levels of the proinflammatory cytokine tumor necrosis factor-α are observed in the olfactory epithelium of patients with COVID-19 infection. Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF- α) are identified as prominent biomarkers for COVID-19 progression; and their levels in the plasma associate with viral replication, respiratory and systemic symptoms, such as musculoskeletal involvement (fatigue, malagia, arthralgia) (Cipollaro *et al.,* 2020).

In our study, more male patients in the age group between 35-55 years and more mild cases from the urban areas had COVID-19 infection. In total, 35 (63.6%) of the severe patients were males (Zhang *et al.,* 2020a). Symptomatic patients of COVID-19 can have any of the typical symptoms of COVID-19 i.e., fever, cough, fatigue, anorexia, shortness of breath, sputum production, muscle pain etc. (Mao *et al.,* 2020). It was observed a significant correlation of the disease severity with the family source of exposure. COVID-19 in the elderly and especially in males, is more likely to result in severe alveolar damage and respiratory failure. Also, the healthcare workers and family members are high risk populations (Chen *et al.,* 2020a; Chen *et al.,* 2020b). The patients of our study showed low lymphocytes (80%), high neutrophils (70%), low hemoglobin (61%) and high white blood cell count (WBC) (25%). Recent reports have shown that a proportion of COVID-19 patients presented with the elevated leukocyte count (Zhao *et al.,* 2020a&b). It was reported that as compared with survivors, the non-survivors had higher leukocyte counts, more elevated neutrophil counts, smaller lymphocyte counts and lower platelet counts (Zhao *et al.,* 2020b). We reported that the disease severity was found significantly and strongly correlated with decreased oxygen saturation level. Leucopenia and lymphopenia result in part from the effect of inflammatory cascade as well as the viral activity at bone marrow level. High mortality has been seen in COVID-19 patients who were having significant lymphopenia (Li *et al.,* 2020). Other blood cells, including WBC, neutrophils and platelets, can be discriminated predictors in differentiating mild from severe cases of COVID-19 (Velavan and Meyer, 2020). A study reported that in COVID-19 patients, the hypoxemia was found to have a link with the mortality (Xia and Lazartigues, 2020).

We found that the severity was significantly associated with the elevated levels of urea, creatinine and LDH. COVID-19 patients can frequently show signs of liver dysfunction i.e. increase in ALT and AST as well as renal dysfunction reflected by raised urea and creatinine (Lian *et al.,* 2020). Viral activity induces several inflammatory and hematological changes that can induce acute liver and renal injuries, leading to the increased levels of these enzymes. Severe COVID-19 patients can more frequently have lymphopenia, higher levels of ALT, AST, LDH, CRP, ferritin, and D-dimers as well as markedly higher levels of Interleukins (Chen *et al*., 2020a &b). Raised LDH levels have been found associated with the development of severe disease and mortality in patients with COVID-19 (Henry, 2020). CRP, lymphopenia and raised LDH have been significantly linked with the severe COVID-19 cases (Zhang *et al.,* 2020b). Among coagulation parameters, the common findings are related to the significant elevation of plasma D-dimers & fibrin degradation products, and modest increase in prothrombin and activated partial thromboplastin times (PT/aPTT) (Connors and Levy, 2020 a&b). In current study, it was also found that the disease severity was significantly correlated with the raised levels of both D-dimers and other tissue markers. D-dimer levels were found four times higher in severely affected patients compared to non-severe patients (Tang *et al.,* 2020). It is found that D-dimer elevation is the strongest independent predictor of mortality (Schutgens, 2020). The main comorbidities in our patients were hypertension, diabetes mellitus and cardiovascular disease. In a multi-center study, 48% COVID-19 patients had a co-morbidity, with hypertension being the most common (30%), followed by diabetes mellitus (19%) and cardiovascular disease (8%) (Zhou *et al.,* 2020). Main complications of COVID-19 in our study population were acute liver injury (18%), acute renal injury (14.8%) followed by myocarditis (12%) (Chen *et al.,* 2020a&b).

CONCLUSION

The altered levels of different biochemistry can impact the neurological states of COVID-19 patients. Therefore, it is recommended to monitor these biochemistry and tissue marker parameters on a routine basis. There is a need to investigate more exact involvement and efficacy of biochemistry in determining the neurological impacts in detail.

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